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Weakness in the Critically Ill: "Captain of the Men of Death" or Sign of Disease Severity?

After overcoming numerous complications, critically ill patients often experience profound muscle weakness. The subsequent need for prolonged mechanical ventilation, and their physical disability, can render victory over those conditions hollow.

In recent years, our understanding of how mechanical ventilation harms respiratory muscles has advanced tremendously. Studies have demonstrated a correlation between duration of mechanical ventilation and diaphragmatic atrophy, sarcomere injury, decreased diaphragmatic fiber specific force, and up-regulation of atrophic genes (*Atrogin1* and *MuRF1*) (1, 2).

Critical illnesses can harm muscles other than respiratory muscles (3, 4), risking long-term disability and even mortality (5). Puthucheary and colleagues (3) reported reduction in rectus femoris area during the first week of critical illness. The decrease was greater in patients with multiorgan (vs. single-organ) failure, and in patients fed with greater quantities of protein. The pattern of intracellular signaling supported increased muscle breakdown and decreased synthesis. Similar results were reported by Wollersheim and colleagues (4), who also noted a rapid decrease in myosin heavy-chain mRNA and increased expression of *Atrogin1* and *MuRF1*.

In this issue of the *Journal* (pp. 57–66), Dres and colleagues (6) extend our knowledge on the prevalence and implications of muscle weakness in critically ill patients deemed ready for their first weaning trial. Two-thirds of the 76 patients had diaphragmatic weakness. One-third had limb weakness. In contrast to previous reports (7), diaphragmatic weakness was not associated with sepsis, but was associated with longer ventilator duration, more frequent weaning failure, and higher mortality. Limb weakness was associated with longer ventilator duration and longer hospital stay. Diaphragmatic weakness was primarily evaluated using twitch tracheal pressure (Ptr,stim) elicited by magnetic stimulation of the phrenic nerves. Limb weakness was evaluated with the Medical Research Council (MRC) score.

On the basis of the new study, can we state with certainty that respiratory and limb muscles respond differently to critical illness? This is an important question if we are to tailor the development of therapies to one muscle group or the other.

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Despite known associations between respiratory and limb muscle weakness (8), it remains biologically plausible for respiratory and limb muscles to respond differently to critical illness—the former being more likely than the latter. In rabbits, controlled mechanical ventilation (CMV) causes injury to the diaphragm but not to soleus myofibers (9). In patients, CMV produced diaphragmatic atrophy without impacting extradiaphragmatic muscles (10). Moreover, CMV up-regulates *Atrogin1* and *MuRF1* genes, and induces the autophagy–lysosome pathway (11). In the quadriceps of these patients, Atrogin1 induction is modest and MuRF1 is absent. Few autophagy-related genes are expressed above control levels (11).

More controversial is the proposed mechanistic association between respiratory weakness and weaning failure. Dres and colleagues (6) found an association between the two, whereas Laghi and colleagues (12) did not. Can these conflicting results be reconciled? Dres and colleagues (6) measured Ptr,stim as a surrogate for transdiaphragmatic twitch pressure (Pdi,stim). Laghi and colleagues (12) measured Pdi,stim directly (although Ptr,stim and Pdi,stim are correlated [13, 14]). Of greater importance than what was measured, is how it was measured and how it was verified. To obtain accurate twitch pressures, stimulating probes must be in close proximity to the phrenic nerves (12). Rigorous strategy is imperative to achieve this goal: one nerve is stimulated at a time while monitoring electromyography and pressure (13, 14). Once the probe has been positioned where it elicits the strongest signal, investigators repeat the process on the other phrenic nerve. Only then are bilateral stimulations delivered. Verification to ensure supramaximal stimulation is also required (12) because low twitch pressures may simply reflect submaximal stimulation rather than weakness. Watson and colleagues (14) found that Pdi,stim was 10.8 cm H_2O in patients with supramaximal stimulation and 8.4 cm H_2O in patients with submaximal stimulation. They achieved supramaximality with certainty in only 75.8% of patients. Dres and colleagues (6) were not able to test for supramaximality because the ethics committee allowed them to deliver no more than five bilateral stimulations at a single stimulating power output (M. Dres and A. Demoule, personal communication). Thus, we do not know what proportion of the small twitches signified weakness as opposed to being the result of insufficient magnetic stimulation.

Another explanation for the contrasting results might be a type II error in the smaller study by Laghi and colleagues (12). This seems unlikely considering that in a study of 100 patients,

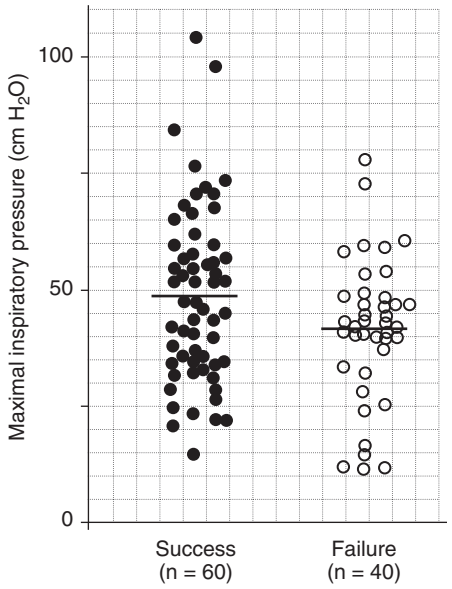

Figure 1. Maximal inspiratory pressure recorded before a weaning trial in 60 weaning-success patients (*solid symbols*) and 40 weaning-failure patients (*open symbols*). Maximal inspiratory pressure did not differ significantly between the groups. The *horizontal bars* represent mean values. Data from Reference 15, courtesy of Martin J. Tobin.

Yang and Tobin (15) found no difference in maximum inspiratory airway pressure (MIP) between weaning-failure and weaning-success patient groups (Figure 1). MIP is a voluntary maneuver and depends on patient cooperation—as does the more complex MRC score used by Dres and colleagues (6). Therefore, if we ignore the MIP data solely because of the need for patient participation (15), then we should ignore the MRC data of the newer study as well (6).

Dres and colleagues (6) confirm a possible association between limb weakness and longer ventilator duration and length of stay (5, 8). Strategies to improve limb muscle weakness in critically ill patients, with an aim to decrease hospital length of stay, however, have produced varying results (16).

There is no question that respiratory muscle weakness is important, but it is weakness in combination with other equally important, yet too often ignored factors that impact weaning outcome. These factors include changes in pulmonary mechanics during trials of spontaneous breathing and, possibly, decreased respiratory muscle endurance. The investigation by Dres and colleagues (6) also points to the need for studies to identify the mechanisms, if any, linking limb muscle weakness with ventilator duration and hospital length of stay. Until we know whether muscle weakness is either the "captain of the men of death" or a marker of disease severity, intensivists should strive to limit the duration of mechanical ventilation and bed rest, while aggressively treating and preventing sepsis. ■

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The Bumpy Road for Noninvasive Ventilation in Acute Respiratory Distress Syndrome

Coming to an End?

Noninvasive ventilation (NIV) has gained wide acceptance as a treatment for hypercarbic respiratory failure, but its application in patients with hypoxemic respiratory failure, with the exception of those with cardiogenic pulmonary edema or chest trauma, has been challenging (1). The application for acute respiratory distress syndrome (ARDS) has even been termed "the final frontier" for NIV to treat acute respiratory failure (2). Reports on its application in ARDS are few, and those available have shown high failure rates. In their 2001 survey on use of NIV to treat acute hypoxemic respiratory failure, Antonelli and colleagues (3) observed an NIV failure rate almost fourfold higher for ARDS and pneumonia than for other forms of hypoxemic acute respiratory failure.

A number of reasons likely explain the challenges of applying NIV to patients with ARDS. For one, patients with ARDS are tachypneic and breathe at high minute volumes, making it difficult for NIV ventilators to keep up and synchronize. Also, the severe hypoxemia and stiff lungs seen in these patents often necessitate high levels of positive end-expiratory pressure and pressure support. These high pressures promote air leaks around the mask, contributing further to patient–ventilator dyssynchrony and requiring greater strap tension to control the air leaks, intensifying mask discomfort and contributing to intolerance. In addition, patients with ARDS often have underlying processes, such as pneumonia, sepsis, and multiorgan dysfunction, that may progress to the point where NIV is no longer sufficient to support oxygenation or stability. If needed intubation is delayed under these circumstances, unanticipated respiratory arrest can occur, adding to morbidity and mortality.

Some prior attempts at applying NIV in ARDS have suggested that there may be a subgroup of patients who benefit. Antonelli and colleagues (4) described the use of NIV as a "first line intervention" for ARDS in a prospective cohort of patients, demonstrating avoidance of intubation in 54% of patients with ARDS admitted to the intensive care unit (ICU). Those failing NIV had much higher rates of ventilator-associated pneumonia and mortality than those who succeeded and could be identified by having Simplified Acute Physiology Score II greater than 34 and Pa_{O_2}/FI_{O_2} less than or equal to 175 after the first hour of NIV. However, the 54% of patients who succeeded with NIV in the ICU was calculated without including in the denominator the two-thirds of patients who were intubated before ICU admission. Thus, only some 15% of patients in the entire cohort actually succeeded with NIV therapy.

A subsequent small randomized controlled trial (RCT) on patients with "early" ARDS (Pa_{O_2}/FI_{O_2} between 200 and 300) showed that NIV reduced the need for intubation and the number of organ failures compared with conventional O_2 therapy (5). More recently, NIV administered via a full face mask was compared with high-flow nasal oxygen (HFNO) and standard oxygen in a three-way randomized controlled trial (6) on patients with ARDS ($Pa_{O_2}/FI_{O_2} <$ 300). Although the main outcome, intubation rate, was not different in the whole cohort, it was significantly lower with HFNO in the subgroup with Pa_{O_2}/FI_{O_2} less than 200.

In this issue of the *Journal*, Bellani and colleagues (pp. 67–77) report on the use and outcomes of NIV to treat ARDS in LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) (7). This study prospectively collected data over 4 weeks on 2,813 patients with ARDS ($Pa_{O_2}/FI_{O_2} < 300$ and new bilateral infiltrates) in 459 ICUs in 50 countries throughout the world (8). A total of 507 patients (18%) were managed with NIV on Day 1, and 436 (15.5%) continued on Day 2. The latter cohort was stratified into mild, moderate, and severe ARDS subgroups. Rates of NIV use did not differ between the three subgroups (14.3, 17.3, and 13.2%), whereas mortality rates did (22.2, 42.3, and 47.1%, respectively). As also reported by many others, NIV failure was associated with a much higher mortality than NIV success: 45.4 versus 16.1%, respectively. A propensity-matched analysis also detected a higher ICU mortality among patients with a Pa_{O_2}/FI_{O_2} less than 150 treated with NIV (36.2%) than in those treated invasively (24.7%).

The study by Bellani and colleagues is one of the largest cohorts of patients with ARDS treated with NIV yet reported, and another strength is the systematic prospective data collection on patients with well-defined ARDS (7). Weaknesses include the collection of physiologic data only once daily, the lack of data on interfaces or the duration of use, and the exclusion from analysis of patients treated with NIV only on Day 1, thus missing early failures and lowering the reported NIV failure rate. Furthermore, data on use of HFNO were not collected.

Prior studies on the use of NIV for ARDS have been limited by the unreliability of ARDS diagnosis. A North American study using physician diagnosis found no use of NIV for ARDS but 40% use in patients diagnosed with pneumonia, some of whom probably also had ARDS (9). In the study by Bellani and colleagues (7), the overall rate of NIV use for ARDS (18%) seems suitably low,